Critical Care Nephrology and Acute Kidney Injury

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The Intensivist's Perspective of Shock, Volume Management, and Hemodynamic Monitoring

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Abstract

One of the primary reasons for intensive care admission is shock. Identifying the underlying cause of shock (hypovolemic, distributive, cardiogenic, and obstructive) may lead to entirely different clinical pathways for management. Among patients with hypovolemic and distributive shock, fluid therapy is one of the leading management strategies. Although an appropriate amount of fluid administration might save a patient's life, inadequate (or excessive) fluid use could lead to more complications, including organ failure and mortality due to either hypovolemia or volume overload. Currently, intensivists have access to a wide variety of information sources and tools to monitor the underlying hemodynamic status, including medical history, physical examination, and specific hemodynamic monitoring devices. Although appropriate and timely assessment and interpretation of this information can promote adequate fluid resuscitation, misinterpretation of these data can also lead to additional mortality and morbidity. This article provides a narrative review of the most commonly used hemodynamic monitoring approaches to assessing fluid responsiveness and fluid tolerance. In addition, we describe the benefits and disadvantages of these tools.

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Introduction

Circulatory shock, a mismatch between oxygen delivery and consumption, is associated with high mortality and morbidity if not corrected early (1). Therefore, shock can lead to single-organ or multiorgan failure, particularly in those organs with high oxygen demand. Among patients with all types of shock, altered mentation, decreased urine output, increased lactate production, and skin changes (for example, mottled skin and increased capillary refill time in hypovolemic and distributive shock but cold and clammy skin in cardiogenic shock) are common findings. Depending on the type of shock, the underlying predominant pathophysiologic mechanism differs. The four major shock types are as follows. (*1*) Hypovolemic shock (16% frequency) results from internal or external volume or blood loss and usually resolves with timely and adequate intravenous volume replacement. (2) Cardiogenic shock (16% frequency) is related to myocardial (pump) failure due to arrhythmias, increased filling pressure, or decreased myocardial contractility. (*3*) Distributive shock (62% frequency) is related to clinically significant vasodilation and inflammation (for example, in patients with sepsis, adrenal or thyroid insufficiency, or anaphylaxis). (*4*) Obstructive shock (2% frequency) arises from a blockage within the circulation (*e.g.*, thrombus, tumor, or air) or external compression (*e.g.*, cardiac tamponade or tension pneumothorax) (1) (Table 1). Other shock types (for example, neurogenic) are less frequent and will not be discussed here.

In cardiogenic and obstructive shock, reduced cardiac output is the underlying pathophysiologic mechanism that leads to circulatory failure. In contrast, relative and/or absolute intravascular volume depletion is the primary reason for distributive and hypovolemic shock clinical manifestations. Therefore, fluid and vasopressor therapy is considered the cornerstone of resuscitation of hemodynamically unstable, critically ill patients with both hypovolemic and distributive shock. About 50% of hemodynamically unstable patients respond to a fluid challenge by increasing stroke volume and cardiac output (2). (Hemodynamic instability indicates a state in which there are abnormal or changing hemodynamic variables that themselves may lead to a local and global hypoperfusion.) Although restoring and replacing intravascular volume during shock are essential, a growing evidence base suggests that unnecessary fluid administration is harmful and carries an increased risk of multiorgan failure. Therefore, it is crucial during the resuscitation phase of all critically ill patients to determine when to stop giving fluid and when to start de-escalation. Kidneys are among the most sensitive organs to changes in hemodynamic status during an episode of physiologic shock. Although decreased blood effective volume often leads to AKI, hypervolemia (leading to venous congestion) is also a major risk factor for kidney failure (3). Depending on the underlying type of shock, decreased effective blood volume, kidney congestion, nephrotoxin exposure, and excessive inflammatory response are all recognized causes of AKI (4). Therefore, appropriate management of shock can not only prevent the development of moderate to severe AKI, but it can also lead to fewer long-term adverse effects on kidney function and thus a

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Table 1. Different shock types (84)

Type	Etiology	Mechanism	Example	Preload	Cardiac Output	Systemic Vascular Resistance	Filling Pressure	Management
Hypovolemic	Decreased effective blood volume	Blood loss, body water loss	Exsanguination; internal bleeding; external: diarrhea, excessive sweating; internal: third spacing, capillary leak	↓	↓	↑	↓	Fluid therapy: crystalloids, colloids, blood products
Cardiogenic	Arrhythmia, decreased contractility	Bradyarrhythmia/ tachyarrhythmia cardiomyopathy	VT/A-fib with RVR, ischemic CM	↑	↓	↑	↑	Antiarrhythmics, inotropics
Distributive	Vasodilation	Low systemic vascular resistance	Sepsis, anaphylaxis, endocrine: adrenal insufficiency	↓/↔	↑	↓	↓	Fluid therapy, vasopressors, treating underlying source
Obstructive	Circulatory blockage	Internal blockage, external compression	Pulmonary embolism, tension pneumothorax, tamponade, tumor	↑	↓	↑/↔	↓/↔	Resolution of obstruction

VT, ventricular tachycardia; A-fib, atrial fibrillation; RVR, rapid ventricular response; CM, cardiomyopathy.

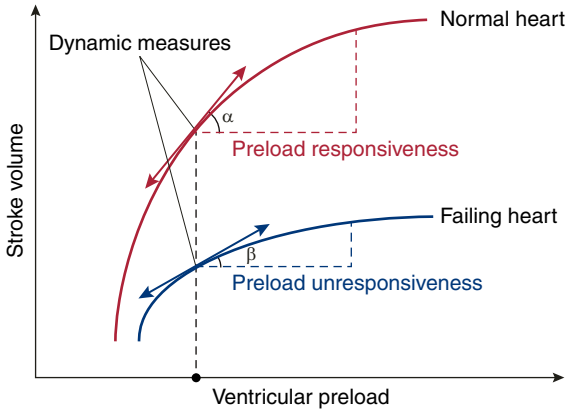

Figure 1. | Fluid responsiveness on the basis of myocardial contractility. These Frank–Starling curves show two patients with normal and failing hearts. The normal heart can increase its stroke volume by preload expansion, whereas the failing heart cannot. Using a static measurement for fluid status by assessing ventricular preload (estimated by central venous pressure), two patients may have similar preload but completely different responses to fluid loading. However, dynamic measurements can assess the steepness of the curves (*i.e.*, α- and β-angles) and identify if patients are fluid responsive or not (here, α is larger than β, indicating a higher increase in stroke volume for a given fluid bolus).

lower rate of CKD (5). This article will describe the current recommendations regarding fluid therapy and how hemodynamic monitoring tools can optimize assessment and management of intravascular volume among critically ill patients with hypovolemic and distributive shock.

Optimizing Fluid Resuscitation

The Frank–Starling curve describes the ability of the heart to change its force of contraction in response to a change in myocyte length (preload). As such and depending on the functional integrity of the underlying myocardium, stroke volume will change to a greater or lesser extent in response to any given change in venous return (Figure 1). Increased venous return in a normal heart with normal function and stable afterload will increase stroke volume by increased stretch of the cardiac myocyte (sarcoma-length) cells. This increases subsequent systolic force generation and enables the heart to eject additional blood, thus increasing stroke volume. Patients "operating" on the flat part of the curve are less sensitive to changes in preload and intravenous fluid bolus administration, indicating a lack of fluid responsiveness. In this situation, it has been suggested that extravascular lung water increases in patients who are less fluid responsive, which manifests clinically as pulmonary edema (6). In contrast, patients operating on the steep portion of the curve are very sensitive to changes in preload (*i.e.*, they are volume responsive) and will exhibit an increase in stroke volume and cardiac output in response to a fluid bolus.

Although these physiologic concepts were described many years ago, they permit an understanding of the intricate relationship between preload, stroke volume, and cardiac output. Coupling an assessment of volume responsiveness considering both afterload and the systolic contractile state of the patient's heart will determine the effect of a given fluid bolus on cardiac output. It will, thus, help determine the best approach to the management of shock.

An optimal resuscitation strategy balances the need to restore adequate stroke volume to improve tissue perfusion (and oxygen delivery) while avoiding hypervolemia, leading to complications associated with venous congestion and interstitial edema. Although intravascular fluid expansion can be lifesaving in the short term, it is important to remember that not every fluid-responsive patient is hypovolemic and may not necessarily require volume expansion. In brief, volume responsiveness does not equal volume deficiency.

Systemic Venous Congestion

Organ perfusion is affected by systemic arterial BP, intravascular volume status, cardiac output, and venous pressure (7,8). At the tissue level, the pressure gradient across the capillary bed is important for optimal perfusion (9). Volume overload, congestive heart failure, and kidney failure are three common causes of venous congestion. Growing evidence indicates a negative effect of venous congestion on clinical outcomes (10), which affects every organ (11). Pulmonary edema, chest wall edema, and prolonged ventilation are examples of these effects on the lungs. Other detrimental effects include hepatic congestion, abdominal compartment syndrome (12), abdominal wall edema, ileus, renal interstitial edema, diastolic dysfunction, and intrinsic myocardial depression (13–15). There is growing evidence that volume overload, kidney hyperemia, or increased pressure in the kidney capsule results in AKI (16–19). The pressure gradient that drives ultrafiltration in glomeruli is roughly 10–15 mm Hg (20). Intrarenal hypertension can increase the pressures in interstitial tissues around the peritubular capillaries. A subtle increase in the interstitial pressure could significantly reduce peritubular capillary perfusion and lead to tubular ischemia. Kidney hyperemia, congestion, or edema can occur both as a direct result of shock and also as a result of its management (13). There is a well-described relationship between venous congestion, increased kidney volume (21), and intrarenal hypertension (13). Indeed, increasing central venous pressure (CVP) is one of the strongest predictors of worsening kidney function among all other hemodynamic variables (22). Venous congestion (23,24) can occur as a result of aggressive volume resuscitation (25), heart failure (26,27), pulmonary hypertension, or sepsis (28–30). Minimizing kidney congestion and intra-abdominal hypertension can also mitigate the risk of AKI and/or expedite its recovery (31,32).

Fluid Management Strategies

The "4 D's" of fluid therapy (drug, duration, dose, de-escalation) (11) are important concepts that vary during different stages of shock management. These have also been termed salvage, optimization, stabilization, and de-escalation (1). The cornerstone of shock management is choosing the most appropriate fluid type and delivering it at the correct rate (in an appropriate amount), with a plan to remove it when recovery begins.

Fluid administration strategies vary from strict protocolized approaches to more nuanced and individualized

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treatment plans and range from conservative (dry) to liberal (wet) fluid administration strategies. By way of example, CVP targets might average 4–8 cm H_2O in a conservative approach versus 8–12 cm H_2O in a liberal strategy. The key (and still unanswered) question is which of these strategies leads to the best clinical outcomes.

Fluid strategies have evolved over the last two decades. In 2001, Rivers *et al.* (33) reported on a single-center, randomized controlled trial of early goal-directed therapy versus usual care in patients with septic shock in a US urban emergency department. Early goal-directed therapy constituted a 6-hour resuscitation protocol for administration of intravenous fluid, vasopressors, inotropes, and red blood cells to achieve a prespecified target for arterial BP, CVP, central venous oxygen saturation, and hemoglobin level. Mortality in that trial was reportedly lower in the intervention group (31% versus 47% in the control group), prompting many institutions worldwide to adopt this early goal-directed therapy approach.

Three other studies (ARISE [34], PROCESS [35], and PROMISE [36]) challenged the early goal-directed therapy paradigm (Supplemental Table 1). These studies compared early goal-directed therapy with usual care and found no difference in mortality. In 2017, a meta-analysis of individual patient data from these three multicenter trials was designed to improve statistical power and explore the heterogeneity of treatment effect of early goal-directed therapy (37). Early goal-directed therapy was associated with a greater need for intensive care and cardiovascular support than usual care. Other outcomes did not differ significantly, although average costs were higher in the early goal-directed therapy groups. Subgroup analysis showed no benefit from early goal-directed therapy for patients with more severe shock or in hospitals with a lower propensity to use vasopressors or fluids during usual resuscitation (37).

Furthermore, in another study comparing two fluid management strategies in the setting of acute lung injury, patients randomized to a fluid conservative strategy had significantly more ventilator-free days and shorter lengths of stay than the liberal fluid strategy group. Still, no difference in mortality was found (38). Indeed, in another randomized trial, authors found significantly less worsening kidney function when the ultraconservative fluid strategy was compared with the current standard of care (39). Myles *et al.* (40) compared conservative versus liberal fluid management in the perioperative period among patients who underwent major abdominal surgeries. Although the primary outcome (*i.e.*, disability-free survival at 1 year) was not different, patients in the liberal intravenous fluid group experienced less AKI and wound infection (40).

In summary, a conservative fluid management strategy seems to be associated with lower cost, shorter length of stay in the intensive care unit (ICU), and more ventilator-free days without affecting mortality.

End Points of Resuscitation

End points of resuscitation are important to guide therapy. During acute critical illness, rapid restoration of perfusion pressure is a priority. Unfortunately, no single marker guarantees adequate oxygen delivery or organ perfusion. Traditionally, urine output, serum lactate level, and mean arterial pressure are followed and monitored to guide and assess resuscitation; however, the optimal end point of resuscitation remains controversial. Therefore, there is a need for a multimodal approach that combines different parameters, including cardiac output and assessment of venous congestion (41).

Assessment of Fluid Status

A thorough assessment of fluid status is essential to optimize effective blood volume and cardiac output while avoiding volume overload. A comprehensive fluid status evaluation requires information regarding the macrocirculation (effective blood volume; mean systemic filling pressure [42,43] and mean arterial pressure; cardiac contractility; liver, kidney, and bowel compartmental pressures; and intra-abdominal and intrathoracic pressures) and the microcirculation (capillary permeability and perfusion, glycocalyx layer integrity, and tissue edema). (The mean systemic filling pressure is defined as the mean pressure that exists in the circulatory system when there is no blood motion. The difference between mean systemic filling pressure and right atrial pressure determines blood return to the right atrium.) The complexity of this assessment makes it very challenging. Despite this, intensivists do now have access to an array of tools that can better approximate a patient's actual intravascular and interstitial volume status (Figure 2).

History, Physical Examination, and Biomarkers

Obtaining a comprehensive history should identify the dominant shock type, which, in turn, may be used to strategize fluid management (*e.g.*, fluids for hypovolemic and distributive shock states and no or limited fluids for obstructive and cardiogenic shock states).

Physical signs of shock include altered mentation (44), increased capillary refill time (45), or mottled skin (46), and these can be used for prioritization purposes. In addition, signs of central venous congestion (*e.g.*, jugular vein distention, edema, and pulmonary rhonchi [10]) generally indicate intravascular volume overload; pallor, reduced skin turgor, and sinus tachycardia usually point to a need for intravascular volume expansion.

Measurement of serum biomarkers of perfusion, such as lactate and renin, might also provide a means of highlighting the urgency of therapeutic intervention among patients with circulatory shock (47,48).

Among patients with circulatory shock, acute and chronic kidney dysfunction is common, and circulatory shock also leads to kidney dysfunction if left uncorrected. As kidneys are very sensitive to inadequate perfusion, low urine output and worsening kidney function can manifest as markers of hypoperfusion. As such, urine output and kidney function typically improve with appropriate resuscitation. Indeed, urine output–guided fluid therapy is associated with significantly lower rates of AKI in some settings (49). Therefore, it is important to highlight the specific role of kidney failure in shock monitoring and assessment. Several kidney dysfunction complications can affect circulatory shock management, including acid-base imbalances leading to changes in respiratory drive and response to

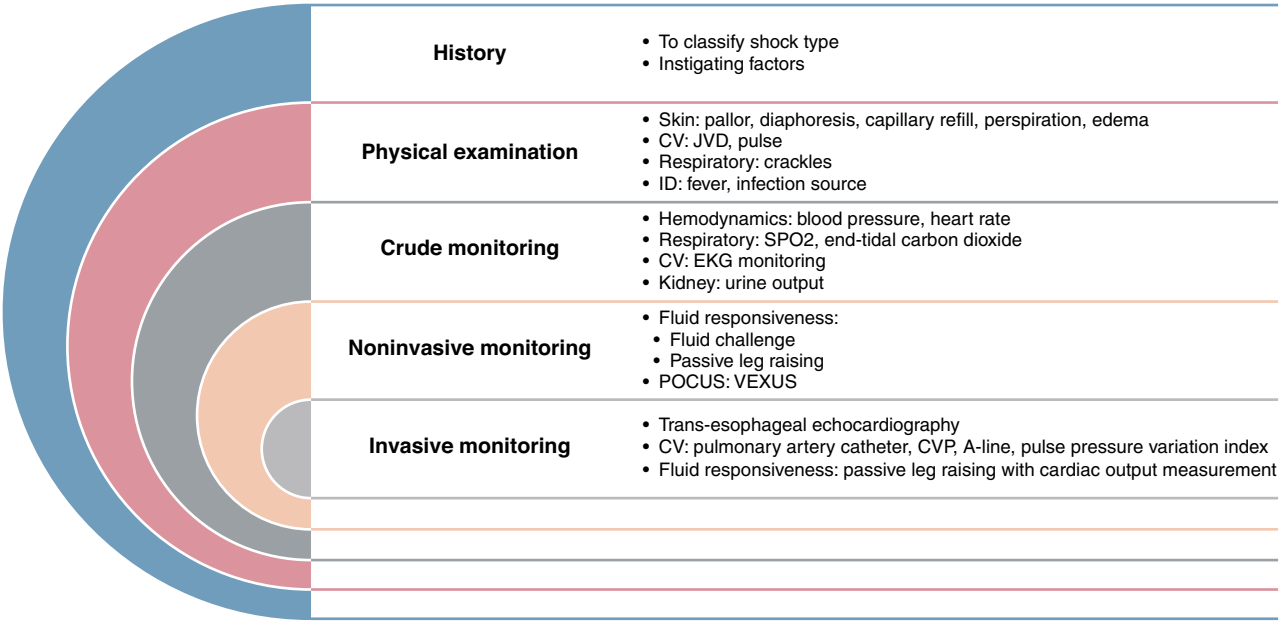
History
• To classify shock type
• Instigating factors
Physical examination
• Skin: pallor, diaphoresis, capillary refill, perspiration, edema
• CV: JVD, pulse
• Respiratory: crackles
• ID: fever, infection source
Crude monitoring
• Hemodynamics: blood pressure, heart rate
• Respiratory: SPO2, end-tidal carbon dioxide
• CV: EKG monitoring
• Kidney: urine output
Noninvasive monitoring
• Fluid responsiveness:
• Fluid challenge
• Passive leg raising
• POCUS: VEXUS
Invasive monitoring
• Trans-esophageal echocardiography
• CV: pulmonary artery catheter, CVP, A-line, pulse pressure variation index
• Fluid responsiveness: passive leg raising with cardiac output measurement

Figure 2. | **Major components in and tools for shock evaluation.** CV, cardiovascular; CVP, central venous pressure; EKG, electrocardiogram; ID, infectious diseases; JVD, jugular venous distention; POCUS, point-of-care ultrasound; SPO2, saturation of peripheral oxygen; VEXUS, venous excess ultrasound grading system.

vasoactive agents; electrolyte derangements resulting in arrhythmia, myocardial dysfunction, muscle weakness, and rhabdomyolysis; vascular tonicity; coagulation disorders (*e.g.*, hypercoagulability and platelet dysfunction); reduced toxin/drug elimination (*e.g.*, digoxin and vancomycin); and fluid retention (50).

Monitoring

Crude monitoring tools are routinely used in shock management and fluid administration decision-making processes. These monitoring variables include continuous recording of BP, heart, and respiratory rates; measurement of oxygen saturation, end-tidal CO_2, and urine output; and continuous electrocardiography. Although these variables are widely available, they often lack sufficient sensitivity and specificity to distinguish volume depletion, euvolemia, and volume overload. More advanced monitoring tools for hemodynamic and fluid status assessments can be divided into noninvasive (*e.g.*, ultrasonography and cardiac output changes in response to a fluid challenge) and invasive (*e.g.*, pulmonary artery catheters or CVP and systemic arterial pressure monitoring *via* indwelling arterial catheter) tools. Invasive tools are associated with complications such as discomfort during placement, infection, and bleeding. Hence, a noninvasive hemodynamic monitor is an appealing concept in both the emergency department and the ICU. A summary of monitoring tools and approaches is provided in Supplemental Table 2.

These devices and techniques produce both static and dynamic variables. Static variables relate to fluid status or responsiveness and are measured intermittently. Dynamic evaluations are measured continuously and typically involve cardiac output monitoring. Dynamic indices of fluid responsiveness have been consistently shown to be superior to static measurements.

Static Measures. When the "spot" filling pressures are measured and interpreted, they are known as static variables. Central filling pressures are presumed to reflect left ventricular end diastolic pressure, a surrogate for left ventricular end diastolic volume (*i.e.*, left ventricular preload.) However, left ventricular end diastolic pressure and volume do not have a linear relationship. Moreover, this relationship is not fixed and can change acutely in patients with coronary hypoperfusion and myocardial dysfunction. Therefore, if filling pressures are used as a surrogate for left ventricular end diastolic volume (preload), they may often lead to misinterpretation of volume status.

The most commonly used static measure in most resuscitation protocols and guidelines is CVP. However, the reliability of CVP for the guidance of fluid management decisions is controversial because of variations in physiology in the case of valvular pathology, right ventricular dysfunction, pulmonary hypertension, and variation in intrathoracic pressure with positive pressure mechanical ventilation. Indeed, a systematic review of 24 studies, including 803 patients, demonstrated a very poor relationship between CVP and effective blood volume and concluded that neither CVP itself nor changes in CVP can predict the hemodynamic response to a fluid challenge (51).

The pulmonary artery catheter was introduced to clinical practice in 1970, after initial development in the 1960s (52,53). A pulmonary artery catheter can be inserted at the bedside without fluoroscopy *via* a central line introducer sheath into the right heart and thence the pulmonary artery, guided by a pressure waveform displayed on the bedside monitor. Pressure information derived from the pulmonary artery catheter includes CVP, right ventricular systolic and diastolic pressures, pulmonary artery systolic and diastolic pressures, and pulmonary artery occlusion pressure (a surrogate for left atrial pressure or left

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ventricular end diastolic pressure). The pulmonary artery catheter can also measure cardiac output using a continuous or intermittent thermodilution technique on the basis of the Stewart–Hamilton equation (54). The utilization of pulmonary artery catheters peaked during the 1980s and 1990s, but its usage has since trailed off due to its invasive nature and subsequent randomized controlled studies that demonstrated no clear outcome benefit. In a randomized controlled trial of 433 patients at 26 sites to determine whether the pulmonary artery catheter is safe and can improve clinical outcomes in patients hospitalized with severe symptomatic and recurrent heart failure, the authors did not find any effect on clinical outcomes, including mortality rates. Indeed, use of a pulmonary artery catheter was associated with a higher incidence of adverse events. However, the trial specifically excluded patients who the investigators thought might benefit from a pulmonary artery catheter. It was also conducted by seasoned physician investigators who were highly experienced in evaluating and managing heart failure (55). In a randomized trial of patients with acute respiratory distress syndrome, using a pulmonary artery catheter in comparison with a protocolized fluid management did not show any benefit. Yet, it was associated with a significantly higher incidence of complications (56). Another cohort study was published in 1996 looking into the association between the use of right heart catheterization during the first 24 hours of ICU admission and subsequent survival, length of stay in intensive care, and cost of care (57). Results showed that right heart catheterization was associated with higher mortality and resource utilization (57). Therefore, in a systematic review of 5051 patients, investigators concluded that the use of a pulmonary artery catheter does not benefit patients or affect clinical outcomes (58).

Despite this, our opinion is that use of CVP and a pulmonary artery catheter by expert clinicians might be helpful in specific circumstances and the proper setting. An example is a patient who has undergone heart surgery or has suffered a right ventricular infarction, acute pulmonary embolism, or cardiac tamponade. In these cases, CVP may be used as a marker of right ventricular function rather than an indicator of volume status. Furthermore, a pulmonary artery catheter can also be used in mixed shock states or instances when other diagnostic evaluations are less informative. Indeed, cardiothoracic surgeons, intensivists, and anesthesiologists familiar with the use of CVP and pulmonary artery catheter, as well as their limitations, can recognize inaccurate trends and adjust their treatment plans accordingly. It is indeed possible that the pulmonary artery catheter may enjoy something of a renaissance with the currently increasing incidence of right heart dysfunction, this time specifically for guidance in managing right heart physiology rather than left-sided cardiovascular function as was previously the case.

Dynamic Measures. Dynamic indices of fluid responsiveness have been consistently shown to be superior to static measures (59,60). Unlike static measurement of filling pressures, dynamic monitoring variables allow an understanding of how the cardiovascular system reacts to changes in circulating blood volume and myocardial preload (61). Although dynamic assessments are more effective than static measures, they are more difficult to assess and often require some preconditions to be reliable. Below, we describe some of the more commonly used dynamic measures.

The fluid challenge test for fluid responsiveness uses rapid delivery of fluids to determine cardiac output changes. In a systematic review, only half of the patients responded to a fluid challenge, whereas the other half did not benefit and were possibly harmed (*e.g.*, volume overloaded) by the challenge (62).

Pulse pressure, the difference between systolic and diastolic arterial BPs, varies with stroke volume changes; therefore, it can be used as a surrogate for stroke volume. Pulse pressure variation with respiratory cycles during positive pressure ventilation occurs due to changes in intrathoracic pressure, which themselves lead to changes in venous return. When patients are fluid responsive, they augment their cardiac output when preload increases. The small changes in preload seen throughout the respiratory cycle lead to variations in stroke volume and thus pulse pressure. Therefore, pulse pressure variation may discriminate fluid responsiveness from those who are fluid refractory by approximating the patient's current position on the Frank–Starling curve. Several studies have demonstrated that measured pulse pressure variation of 13%–15% is strongly associated with volume responsiveness. Pulse pressure variation index is calculated as the ratio of (maximum pulse pressure minus the minimum pulse pressure) to the mean pulse pressure, usually averaged over three or more breaths (63). A caveat is that it is unreliable when patients are not receiving "full" or "passive" mechanical ventilation with at least 8–10 ml/kg tidal volume, have right heart failure, or have arrhythmias associated with beat-to-beat variations (*e.g.*, atrial fibrillation, open chest wound, and patients who have severely reduced lung compliance). Thus, current approaches to pulse pressure variation measurement may only be applicable to specific subpopulations of patients in the ICU (64).

Similarly, stroke volume variation during the respiratory cycle changes when patients are fluid responsive. Therefore, if stroke volume could be measured in mechanically ventilated patients, its variation could be used clinically. Indeed, studies have consistently shown that stroke volume variation of >10% during the respiratory cycle is associated with fluid responsiveness. Stroke volume variation is calculated as the ratio of the maximum stroke volume minus the minimum stroke volume to the mean stroke volume averaged over several respiratory cycles (63). As stroke volume variation during respiratory cycles on mechanical ventilation follows the same limitations as pulse pressure variation, other conditions in which clinicians can actively alter preload could be used as alternatives. These alternatives include but are not limited to the following. (*1*) The first is administration of a fluid challenge during which infusion of a bolus of fluid leads to increased preload. A fluid bolus can increase stroke volume by >10% in some cases among fluid-responsive patients. (*2*) The second is passive leg raising. (The following steps in conducting a passive leg raise maneuver are important for a valid assessment. The process starts with head elevation to about 45°. In this position, the cardiac output is measured. Next, the bed [without touching the patient] is adjusted in order to lower the head to the horizontal position and raise the legs to 45°–60°. Cardiac output is now remeasured in this

position. After returning the patient to the original position, cardiac output is once more assessed to confirm its return to baseline.) Typically, there are about 150–300 ml of blood in the veins of the lower extremities. The passive leg raise maneuver uses this volume to assess the effect of increasing preload on the measured stroke volume (65,66). (3) During 15 seconds of an end expiratory pause in mechanical ventilation, a decline in intrathoracic pressure causes an increase in preload, leading to an increase in stroke volume by >15% among volume-responsive patients (67).

As mentioned above, stroke volume can be measured by both invasive and noninvasive tools. Noninvasive cardiac output monitors use a bioreactance technique that measures the oscillating current during blood passage inside the chest cavity to measure cardiac output. These devices convert changes in the frequency of electrical currents into hemodynamic information, including stroke volume, cardiac output, and stroke volume variation. Unfortunately, several studies have shown low reliability of this technology compared with standard techniques, such as thermodilution (68). In comparison, point-of-care echocardiography can provide a global assessment of ventricular and valvular function and the measurement of stroke volume and cardiac output. Cardiac output may be calculated by determining the velocity-time integral of the spectral Doppler envelope at the left ventricular outflow tract level. The stroke volume can then be calculated using the product of the velocity-time integral and left ventricular outflow tract cross-sectional area and cardiac output by further multiplication of heart rate. Although this is a helpful tool for assessing stroke volume, it has high inter-rater variability and low reliability unless it is done by experienced clinicians (69). Modern ultrasound equipment can automate this process, increasing its reliability.

Inferior vena cava (IVC) diameter variability in mechanically ventilated patients is a dynamic method of intravascular

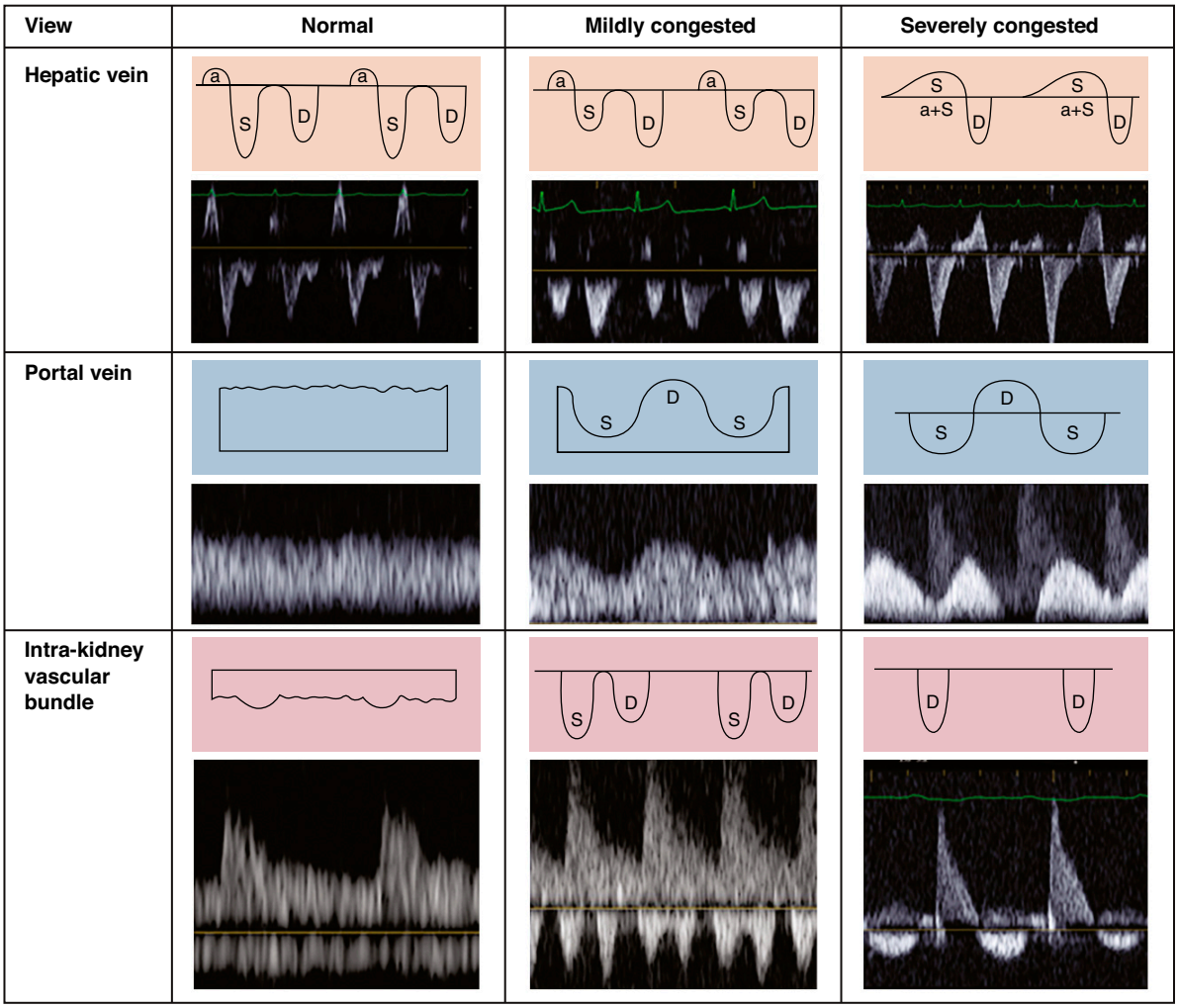

Figure 3. | **Venous flow patterns and organ congestion (76).** Normal hepatic venous flow patterns should have a flow wave larger in systole than in diastole. During progressive liver congestion, the ratio of systolic to diastolic flow continues to decrease, and in severe congestion, the systolic flow becomes reversed. This is due to a progressive decline in right atrial compliance secondary to volume overload. Normally, there is no pulsation in portal venous flow. However, with progressive liver congestion, portal venous flow becomes increasingly pulsatile. Venous flow in the intrarenal parenchymal vessels is also nonpulsatile in normal conditions. This changes with a progressive increase in kidney intracapsular pressure and congestion. In mild to moderate congestion, pulsatile intrarenal venous flow is biphasic, becoming monophasic with progressive congestion (76).

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assessment on the basis of the variation in IVC diameter during the respiratory cycle (70). IVC diameter can be measured at the end of inspiration and expiration using point-of-care ultrasound (POCUS). The distensibility index is calculated as maximum IVC diameter − minimum IVC diameter/minimum diameter, and some modern ultrasound machines provide this as an automated feature. Although IVC distensibility index of >18% is a good indicator of fluid responsiveness, it only has predictive values in a specific subgroup of patients similar to pulse pressure variation and stroke volume variation as described above (71).

Another test indicating the inadequacy of fluid resuscitation during distributive shock is identifying an increased gap between the partial pressure of carbon dioxide in simultaneously drawn venous and arterial blood samples (*i.e.*, ΔPCO_2) (72). This variable is directly related to CO_2 production and inversely associated with cardiac output. When CO_2 production and cardiac output are normal, the ΔPCO_2 is 2–6 mm Hg (73). However, during distributive shock, if cardiac output is low and oxygen delivery is inadequate, the ΔPCO_2 increases to >6 mm Hg. In these conditions, expanding preload instead of vasopressors could lead to improved cardiac output and thus lower the ΔPCO_2 (74,75).

Point-of-Care Ultrasonography in Fluid Status Assessment

During the past decade, the application and utilization of POCUS by intensive care physicians have skyrocketed. Following appropriate training and governance, POCUS can provide timely and critical information. As mentioned above, a global POCUS physical examination of patients in shock can determine fundamental hemodynamic measures (*e.g.*, stroke volume, cardiac contractility, and valvular diseases). In addition, POCUS can assess organ congestion and fluid tolerance (76).

Lung ultrasonography allows estimation of both extravascular lung water and fluid collections in the pleural space. Therefore, a thorough evaluation of lung and cardiac ultrasonography among patients with respiratory failure can lead to a narrower differential diagnosis (77). Doppler interrogation of the portal, hepatic, and intraparenchymal kidney venous flow patterns is a novel measure to assess venous congestion (Figure 3). Blood flows in the portal and intraparenchymal kidney veins are normally nonpulsatile. Several studies have shown that pulsatile flows in these vessels may be a marker of venous congestion and associated with end organ injury (78–81). In hepatic veins, blood flow is affected by the right atrial pressure changes. The systolic blood flow in hepatic veins declines when right atrial compliance decreases due to increased RA pressure. This, in turn, leads to reduced or reversal (from more than one in normal flow to less than one in venous congestion) of the systolic-diastolic hepatic venous flow ratio. In extreme venous congestion, blood flows back toward the liver during systole. A single-center, prospective cohort study of patients undergoing cardiopulmonary bypass surgery showed that portal and intraparenchymal kidney venous flow pulsatility are independently associated with the risk of AKI even after multivariable adjustments, indicating the presence of organ congestion (82). In addition, in a different study, death and heart failure–related readmissions were significantly more common among those with intraparenchymal kidney venous flow pulsatility than those with continuous flows (79).

The venous excess ultrasound grading system (VEXUS) is a grading system using a combination of multiple point-of-care ultrasound markers to assess significant venous congestion, namely IVC diameter and portal, hepatic, and intraparenchymal kidney venous flow patterns. In an investigation of patients after cardiac surgery, the authors reported VEXUS as an independent predictor of postoperative AKI (83). However, the VEXUS grading system is currently not widely used because it is technically challenging and time consuming. Nevertheless, with further clinical validation and determination of its precise role in patient care, simpler versions on the basis of the same physiologic concepts are likely to be adopted into clinical practice, particularly for assessing more complex patients.

Achieving and maintaining euvolemic status among patients with shock are among the primary goals of effective hemodynamic management. However, despite tremendous progress in our understanding of fluid resuscitation and technology, reliably reaching euvolemia continues to remain a challenge. We believe that assessing and considering a combination of variables are likely to improve patient care. These variables include information gained from a careful history and physical examination, static and dynamic hemodynamic measurements, POCUS data, and serum biomarker information. The underlying goal for clinicians remains to identify fluid responsiveness and avoid fluid administration in patients at most risk of fluid overload.

Disclosures

K. Kashani reports consultancy agreements with AM PHARMA; research funding from La Jolla Inc.; honoraria from Nikkiso; patents and inventions with MediBeacon; and serving as a scientific advisor or member of Baxter, GE, La Jolla Inc., and MediBeacon Inc. A.D. Shaw reports consultancy agreements with AM Pharma, Astellas Inc., Edwards Lifesciences, FAST BioMedical, and Novartis; honoraria from AM Pharma, Astellas Inc., Astute FAST, Edwards Lifesciences, and Novartis; and serving as a scientific advisor or member of AM Pharma, Astellas Inc., Edwards Lifesciences, FAST BioMedical, and Novartis. The remaining author has nothing to disclose.

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Author Contributions

K. Kashani and A.D. Shaw conceptualized the study; K. Kashani and A.D. Shaw provided supervision; T. Omer wrote the original draft; and K. Kashani and A.D. Shaw reviewed and edited the manuscript.

Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.14191021/-/DCSupplemental.

Supplemental Table 1. Summary of major multicenter trials related to early goal-directed therapy.

Supplemental Table 2. Comparison of invasive, minimally invasive, and noninvasive cardiac output monitoring tools.

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